UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	**MDL No. 2875**
THIS DOCUMENT RELATES TO ALL CASES	**HON. ROBERT B. KUGLER** **CIVIL NO. 19-2875 (RBK)**

PLAINTIFFS' REPLY BRIEF IN SUPPORT OF *DAUBERT* MOTION TO PRECLUDE OPINIONS OF DEFENSE EXPERT JANICE K. BRITT, PH.D.

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PRELIMINARY STATEMENT

Defendants attempt to evade the methodology applied by Dr. Britt, and to gloss over large gaps in her analysis. Based on her failure to apply a sound methodology, in a reliable manner, and her concessions as to the limits on her knowledge base, Dr. Britt's general causation opinions should be precluded.

LEGAL ARGUMENT

I.

DR. BRITT'S APPLICATION OF EBT WAS METHODOLOGICALLY INADEQUATE

Defendants argue deep within their brief (ECF 1787, p. 17) that Dr. Britt did not apply EBT, the methodology she has been advocating for in the literature, and which she clearly attempted to apply here. Dr. Britt failed to faithfully apply this proposed methodology, violating central tenets that she herself has published; thus, the defense attempted to create the illusion that she did not actually intend to apply EBT. However, they fail to cite to or grapple with Dr. Britt's deposition testimony acknowledging that she applied EBT, and how she did so.[1]

Dr. Britt first explained what EBT is, beginning with identification of a question, "like does chemical X at a certain level cause disease Y," and then the performance of a literature search "[i]f you've got human literature, for example, you would put your – if there's any randomized control trials, you put those first, and then cohort and case-controls." (Britt Dep. Tr., 215:5-218:4, ECF

[1] The secondary problem for the defense is that Dr. Britt could not state that EBT has become an accepted methodology in toxicology, only able to suggest that the "systematic review" component, which EBT borrowed from evidence-based medicine, has started to be incorporated into evaluations by some regulatory bodies, but, "I would have to look at the causation part and see who all, you know, has accepted that as part of their actual assessment process." (Dr. Britt Dep. Tr., 230:5-235:11, ECF 1787-2). The defense agreed that EBT is not applied by regulatory agencies, and to the tertiary problem, the biased intended application of EBT, which the defense acknowledges goes at least to the weight, if not admissibility. (ECF 1787, p. 18-19).

1787-2). Dr. Britt described her attempted application of EBT, "**In this matter in the valsartan context**," first with regard to the levels of human study evidence available:

> Q. **So in this case**, in terms of the hierarchy of human data, which sits at the top according to EBT, there's no RCT, so **you go to the next level, and that would be the cohort studies that you've talked about?**
>
> A. Correct. That's the next in the hierarchy or the pyramid, if you will.

(*Id.* at 240:14-241:20 (emphasis added)). Dr. Britt confirmed that "if you look at number one, on the EBT, …. the valsartan-exposed studies would be, you know the best studies to look at as far as whether or not there's any risk there." (*Id.* at 242:6-243:12). She then agreed to which studies she identified in applying this methodology:

> Q. I'm trying to identify **in terms of your hierarchy in looking at whatever existed in terms of literature**, the Pottegård, Gomm and Al Kindi studies would be the most significant because those are the ones based on cohorts of people that were taking the contaminated valsartan, correct?
>
> A. Correct.

(*Id.* at 243:13-23 (emphasis added)). Dr. Britt's testimony left no doubt that this was her methodology:

> Q. I want to walk through **your methodology** a little more. So we talked about the fact that the human studies would be at the top of the methodology – rephrase. In terms of **your EBT methodology**, we talked about the fact that the human studies, and in particular those studying people who actually took the valsartan with the impurities would be at the top of the hierarchy, correct?
>
> A. Correct.

(*Id.* at 254:3-14 (emphasis added)). The questioning continued, focused on Dr. Britt's application of EBT, and she testified that she considered ranitidine studies. (*Id.* at 254:15-255:14). There was never any question raised during the deposition as to her application of EBT, because that is what

she did—in accordance with her own publication promoting that methodology. *See* James, Britt, Halmes, and Guzelian, *Evidence-based causation in toxicology: A 10-year retrospective*, HUM. EXP. TOXICOL. 34, 1248, 1250 (Dec. 2015) ECF 1704-1, Ex. L).

Defendants attempt to re-write history because Dr. Britt confirmed that she did not faithfully apply the proposed EBT methodology. She testified that a "systematic review" is the linchpin to EBT, agreeing that "when EBT is carried out as intended, part of that process is a systematic review." (Britt Dep. Tr., 228:12-230:4). However, she also conceded that she did not perform a systematic review, which her own article describes as "the primary tool." (*Id.* at 148:3-149:3). Thus, her application of EBT was fatally flawed by definition.

Even more attenuated than Defendants' claim that Dr. Britt did not attempt to apply EBT (ECF 1787, p. 22, n.5), Defendants suggest that the gaping holes in Dr. Britt's methodology are somehow filled by other experts' reports. However, Defendants confuse awareness that other experts existed, with actually relying on those experts' opinions and explaining how and why—which did not occur here. The Third Circuit has affirmed the preclusion of an expert who did far more than Dr. Britt to attempt to rely on other experts. In *In re TMI Litigation*, the Court noted that the expert in question "relied on the opinions of plaintiffs' other dose experts and assumed the correctness of each expert's proposition," but the Court found that was not sufficient, as the expert "never made any attempt to assess the validity of any of the assumptions the other experts used to formulate their opinions." 193 F.3d 613, 714-16 (3d Cir. 1999). Here, Dr. Britt did not even have the other experts' reports when formulating her opinions, and merely inserted placeholders in her report indicating that counsel told her other experts would be writing reports on particular issues.

Dr. Britt's Report does not list other defense expert reports on the list of "Case-Specific Materials I Have Received," and neither does her Report specifically identify any of those reports

or indicate or incorporate any of their findings, because she obviously did not read those reports until after her report was served. (Britt Report, p. 14, ECF 1704, Ex. D). The only reference in Dr. Britt's Report to other defense experts is devoid of any substantive analysis: "[I note that other defense experts in this case will be addressing the epidemiological studies of NDMA/NDEA-exposed individuals in more detail.]" (*Id.* at 29, at 5.1.1.2). In fact, that section of the report provides a list and summary of valsartan and ranitidine epidemiological studies, but does not reference or rely on any other defense expert report. Thus, the defense cannot save Dr. Britt's methodology by focusing on other defense experts' reports that are not discussed or overtly relied on in her report.

Defendants' suggestion that Dr. Britt, "relied on the systematic literature reviews by Defendants' epidemiology experts," (ECF 1787, p. 21), is obviously not true. The starting point is her report, which does not mention a systematic review performed by any defense expert. Dr. Britt could not even say that any other expert actually did perform a systematic review, and could not recall whether any of them claimed in their reports "that they performed a systematic review." (Britt Dep. Tr., 149:4-24). The most she could say about Dr. Fryzek was that "it appeared that he used methods that you would use in a systematic review." (*Id.* at 150:3-16). That is a far cry from relying on a systematic review by another expert, and explaining how and why it was relied on—which did not occur here, as Dr. Britt does not mention or explain any reliance on that expert.

Moreover, addressing the other testimony relied on by Defendants on this point, when asked why she chose to reference "other defense experts" on page 29 as cited above, rather than Plaintiffs' experts, her stated rationale was telling. Aside from not listing those experts' reports in her report because she had not seen them at the time she wrote her report, after saying that she did so because she "agreed more with the methodology of the defense expert," she was completely

unable to describe or distinguish the methodologies applied by Plaintiffs' and Defendants' experts. This eviscerates her claim that she performed a comparison: "I do not recall the specific examples of the differences between the two." (Britt Dep. Tr., 81:21-86:6). Finally, the cases cited by Defendants on this point are completely distinguishable. (ECF 1787, p. 22). In fact, in *Titan Stone, Tile & Masonry, Inc. v. Hunt Constr. Grp., Inc.*, the expert in that case explicitly "incorporated into his report the schedule analysis of an unsworn, undesignated expert." Civ. No. 05–3362 (GEB), 2007 WL 1659056, at *3-4 (D.N.J. June 5, 2007). Dr. Britt did no such thing here. Thus, the fatal gaps in Dr. Britt's application of her methodology cannot be filled by other expert reports she failed to rely on when she reached her opinions.

II.

DR. BRITT FAILED TO ADEQUATELY APPLY DEFENDANTS' FALLBACK METHODOLOGIES

Defendants pivot from EBT, and suggest that Dr. Britt actually applied another unnamed methodology, referring to "Dr. Britt's other methods and opinions." (ECF 1787, p. 14). This cannot be a reference to Bradford Hill, which she did not apply. (Britt Dep. Tr., 261:10-15). Also, at no point in her report or testimony did she state that she applied a weight of evidence methodology, because that is not what she did. Dr. Britt distinguished weight of evidence from EBT and never suggested that weight of evidence was her methodology—describing it as a non-specific approach without concrete parameters. (*Id.* at 225:2-226:21).

Even if Dr. Britt had sought to employ a weight of evidence methodology, her application was still fatally flawed. Defendants make the indefensible claim that Dr. Britt "undertook a thorough review of relevant scientific literature." (ECF 1787, p. 14-15). The review was neither "detailed" nor "thorough." This is because Dr. Britt confirmed that she did not account for important categories of scientific evidence, and recognized that application of a methodology

excluding significant scientific data is not valid: "You should always look at all the evidence and then reach a conclusion based on overall totality and strength of evidence." (Britt Dep. Tr., 176:21-178:7). First, with regard to the dietary studies: "No, I did not look at any of the dietary studies. I did not consider those in my analysis. I looked at them briefly when I was looking at some of the other expert reports. But it was my understanding that the other experts did the evaluation of the dietary studies." (*Id.* at 255:15-256:4). Similarly, with regard to the "mechanistic studies of human tissue," she stated: "[T]hat was not part of anything that I was asked to do. There was other experts that I would defer to for those questions – or those issues." (*Id.* at 257:2-18). The failure to account for key categories of scientific evidence is fatal.

Aside from the human valsartan epidemiology, the only category of evidence Defendants claim that Dr. Britt considered is the animal studies, but she testified: "I looked at the Peto studies. I would defer to other experts as far as the in depth evaluation of animal studies." (*Id.* at 256:11-19). In the absence of any discussion or analysis in her report of how and why she relied on other experts' opinions, she cannot now claim reliance on them. *TMI Litig.*, 193 F.3d at 714-16.

In this connection, Appendix A to Dr. Britt's report is a general discussion regarding extrapolation of animal studies to human risk analysis, which was not prepared for this litigation, and fails to address NDMA and NDEA, or the facts of this case; thus, that discussion has zero to minimal relevance here: "Yeah, it's a general, you know, discussion of extrapolating from animals to humans and sort of some of the shortcomings that have been associated with that type of extrapolation." (Britt Dep. Tr., 257:20-258:13). *See also In re Paoli R.R. Yard PCB Litigation*, 35 F.3d 717, 779, 781 (3d Cir. 1994) (overturning the district court for, in part, "crediting Dr. [Robert

C.]James,[2] … that use of animal studies as a basis for reaching a conclusion on causation of adverse health effects in humans is unreliable," explaining: "the EPA has relied on animal studies to conclude that PCBs are a probable human carcinogen, where there is reason to think that animal studies are particularly valuable because animals react similarly to humans with respect to the chemical in question, and where the epidemiological data is inconclusive and some of it supports a finding of causation, we think that the district court abused its discretion").

In an effort to divert from what Dr. Britt did not do, Defendants point to three factors that a toxicologist should consider, including (1) the need for a "biologically plausible theory," (2) exposure that could lead to absorption, and (3) adequate dose to cause the disease in question. (ECF 1787, p. 12). This illustrates that dose is a factor rather than a methodology in and of itself. The failure to perform a thorough evaluation of the relevant categories of evidence, including the mechanistic and dietary data, fatally undercuts the validity of the analysis.[3]

The defense states that she did consider dose and duration of exposure, attempting to elevate consideration of dose and duration of exposure to a methodology in and of itself. (*Id.* at 11-12, 25-26). What the defense glosses over is that dose and duration of exposure are among numerous relevant factors to be considered. Consideration of dose is not a cure for ignoring important categories of scientific evidence. In other words, dose and duration of exposure need to be taken into account, but along with the other important categories of scientific evidence (as they were by Plaintiffs' experts). Otherwise, the methodology looks at only a limited category of relevant evidence rather than the full picture, resulting in an unsound methodology.

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2 This is the same Dr. James with whom Dr. Britt co-authored *Evidence-based causation in toxicology: A 10-year retrospective*, HUM. EXP. TOXICOL. 34, 1248 (Dec. 2015).

3 The same holds true for Defendants' discussion of background risk and excess cancer risk, which are factors to be taken into account, as they were by Plaintiffs' experts—but not to the exclusion of entire categories of relevant scientific evidence.

Finally, Dr. Britt did not evaluate the regulatory information, and did not "form opinions as to the rightness or wrongness of the regulatory decisions as to whether or to what extent valsartan could be sold with certain levels of contamination." (Britt Dep. Tr., 266:1-12). Dr. Britt did concede that NDMA is a probable human carcinogen. Her testimony was unequivocal: "Q. You would agree with me that the description of NDMA as a probable human carcinogen is accurate, correct? A. Correct." (*Id.* at 199:21-200:2).

III.

DR. BRITT'S CONCESSIONS REGARDING HER QUALIFICATIONS

Dr. Britt cannot testify to matters she agreed she was deferring to others on due to her lack of qualifications on those subjects. Defendants concede that "she is not offering epidemiology or medical opinions." (ECF 1787, p. 8). Dr. Britt's concessions were even more extensive, however, demonstrating a lack of subject matter knowledge:

> Q. [I]n terms of the study design, the strengths and weaknesses, the limitations, any problems or issues with those epi studies, you would defer to the epidemiologist that was retained by the defense. You would really defer to that person on those questions, right?
>
> * * *
>
> THE WITNESS: That's correct. I mean, I can talk about basic high level study problems or study design. But yes, as far as the overall opinions, I will defer to other experts.
>
> BY MR. SLATER:
>
> Q. For example, to the extent there was an issue in the Pottegård study with uncertainty as to whether or not the people on both sides of the study actually fit the criteria and how that would impact a statistical analysis or the strength of the findings, that would be something that I would talk to the epidemiologist about, right?
>
> A. Yes, correct.

(Britt Dep. Tr., 244:1-245:6, 253:16-254:2). It would be unreasonable to allow Dr. Britt to testify

about or in reliance on those studies, since she cannot answer any of the lines of questioning certain to come on cross-examination. *See Leese v. Lockheed Martin Corp.*, 6 F. Supp. 3d 546, 553 (D.N.J. 2014) (citing *Muhsin v. Pac. Cycle, Inc.*, No. 2010–060, 2012 WL 2062396, at *4, *8 (D. Vi. June 8, 2012) ("stating that experts may not rely 'upon opinions developed by another expert without independent verification or validation of the underlying expert's work,' because **Fed. R. Evid. 703 'contemplates that a testifying expert can validate the facts, data and opinions he relied upon ... and be subject to cross-examination on them'**" (emphasis added))). By the same token, Dr. Britt did not address dietary studies or mechanistic studies and admitted that she cannot testify regarding the animal studies in any depth: "I would defer to other experts as far as the in depth evaluation of animal studies." (Britt Dep. Tr., at 255:15-257:18).

Dr. Britt also cannot fall back on any professional experience with NDMA and NDEA to cure her methodological shortcomings. Defendants argue that Dr. Britt worked on a litigated matter with regard to a munitions plant, and performed toxicity calculations for nitrosamines. In fact, Dr. Britt testified that she was only supporting Dr. Robert C. James, her then boss and the author of the report in question. She did not know if the report was served in that case, could not locate any of the documents in connection with that report, and did not say she performed calculations: "I do not recall specifically what I did. It was likely identifying relevant studies related to the toxicity of nitrosamines, NDMA, to review…. [Dr. James] would have reviewed the summaries and reviewed the literature himself to form his opinions for the case." (*Id.* at 41:7-42:24). Dr. Britt's role as a support person in the munitions plant matter is immaterial.

CONCLUSION

For the foregoing reasons, Dr. Britt should be precluded from offering her opinions related to general causation.

Respectfully,

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CERTIFICATE OF SERVICE

I hereby certify that on January 6, 2022, a true and correct copy of the foregoing was filed and served upon all counsel via operation of the CM/ECF system for the United States District Court for the District of New Jersey.

/s/ Adam M. Slater
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